DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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TOSOH BIOSCIENCE, INC.
ROBERT WICK
REGULATORY SPECIALIST
6000 SHORELINE COURT, SUITE 101
SOUTH SAN FRANCISCO CA 94080

October 26,2015

Re: K150270
Trade/Device Name: ST AIA-PACK 25-OH Vitamin D, ST AIA-PACK 25-OH Vitamin D Calibrator Set
Regulation Number: 21 CFR 862.1825
Regulation Name: Vitamin D test system
Regulatory Class: II
Product Code: MRG, JIT
Dated: September 10, 2015
Received: September 14, 2015

Dear Robert Wick:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
k150270

Device Name
ST AIA-PACK 25-OH Vitamin D, ST AIA-PACK 25-OH Vitamin D Calibrator Set

Indications for Use *(Describe)*
ST AIA-PACK 25-OH Vitamin D is designed for in vitro diagnostic use only for the quantitative measurement of total 25-hydroxyvitamin D (25-OH vitamin D) in human serum, Na-heparinized plasma or EDTA plasma on TOSOH AIA System Analyzers. The Tosoh ST AIA-PACK 25-OH Vitamin D is intended as an aid in the determination of Vitamin D sufficiency.

The ST AIA-PACK 25-OH Vitamin D Calibrator Set is intended for in vitro diagnostic use only for the calibration of the ST AIA-PACK 25-OH Vitamin D assay.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

ST AIA-PACK 25-OH Vitamin D
k150270

Date:	**October 22, 2015**
Submitter:	**Tosoh Bioscience, Inc** **3600 Gantz Road** **Grove City, OH 43123**
Contact Person:	**Robert L. Wick** **Regulatory Specialist** **6000 Shoreline Ct., Ste. 101** **South San Francisco, CA 94080** **Phone: 650-636-8117** **Fax: 650-636-8121** **Email: Robert.Wick@Tosoh.com**
Device Name: **Classification:**	**ST AIA-PACK 25-OH Vitamin D** **Class II** **MRG** **Clinical Chemistry** **21 CFR 862.1825**
Device Name: **Classification**	**ST AIA-PACK 25-OH Vitamin D Calibrator Set** **Class II** **JIT** **ClinicalChemistry** **21 CFR 862.1150**
Predicate Device:	**k123131** **Tosoh Bioscience, Inc.** **ST AIA-PACK 25-OH Vitamin D Assay** **ST AIA-PACK 25-OH Vitamin D Calibrator Set**

According to the requirements of 21 CFR 807.92, the following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

Device Description:

The ST AIA-PACK 25-OH Vitamin D is a one-step delayed competitive enzyme immunoassay which, after sample pretreatment, is performed entirely in the ST AIA-PACK 25-OH Vitamin D test cup. Sample pretreatment reagents (containing sodium hydroxide) disassociate 25-OH vitamin D from its binding proteins in the test sample. 25-OH vitamin D present in the pretreated sample is bound to 25-OH vitamin D-specific monoclonal antibody immobilized on magnetic beads. After that, the enzyme-labeled 25-OH vitamin D is added to the reaction mixture. The enzyme-labeled 25-OH vitamin D competes with 25-OH vitamin D for binding to the antibody on magnetic beads in the reaction mixture.

After the second incubation, the magnetic beads are washed to remove the unbound enzyme-labeled 25-OH vitamin D and are then incubated with a fluorogenic substrate, 4- methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled 25-OH vitamin D that binds to the beads is inversely proportional to the 25-OH vitamin D concentration in the test sample. A standard curve is

constructed, and unknown 25-OH vitamin D concentrations are calculated using this curve.

The ST AIA-PACK 25-OH Vitamin D Calibrator Set contains human sera with assigned levels of 25-OH Vitamin D. The calibrator set consists of six calibrators with assigned concentrations of approximately 0, 8, 17, 33, 66 and 135 ng/mL. Each level contains the assigned concentration of the 25-OH vitamin D (described on each vial) with sodium azide as a preservative.

The following products are required to use the ST AIA-PACK 25-OH Vitamin D P/N 025234: ST

AIA-PACK 25-OH Vitamin D Calibrator Set	025334
ST AIA-PACK 25-OH Vitamin D Pretreatment Set	025734

Device Intended Use:

ST AIA-PACK 25-OH Vitamin D is designed for in vitro diagnostic use only for the quantitative measurement of total 25-hydroxyvitamin D (25-OH vitamin D) in human serum, Na heparinized or EDTA plasma on TOSOH AIA System Analyzers. The Tosoh ST AIA-PACK 25-OH Vitamin D is intended as an aid in the determination of Vitamin D sufficiency.

Calibrators:

The ST AIA-PACK 25-OH Vitamin D Calibrator Set is intended for In Vitro Diagnostic Use Only for the calibration of the ST AIA-PACK 25-OH Vitamin D assay.

Device Indications for Use:
Same as Intended Use

Substantial Equivalence:
Comparison between the Tosoh ST AIA-PACK 25-OH Vitamin D (standardized) and Tosoh AIA-PACK 25- OH Vitamin D Assay (unstandardized)

Similarities and Differences

Parameter	**ST AIA-PACK 25-OH Vitamin D Test Cups (modified calibrator)**	**ST AIA-PACK 25-OH Vitamin D Test Cups k123131**
Intended use	ST AIA-PACK 25-OH Vitamin D is designed for in vitro diagnostic use only for the quantitative measurement of total 25-hydroxyvitamin D (25-OH vitamin D) in human serum, Na heparinized or EDTA plasma on TOSOH AIA System Analyzers. The Tosoh ST AIA-PACK 25-OH Vitamin D is intended as an aid in the determination of Vitamin D sufficiency.	Same
Indications for Use	Same as Intended Use.	Same
Sample type	EDTA plasma, Na heparinized plasma or serum	Same
Assay Range	4.0 ng/mL – 120.0 ng/mL	Same
Assay Technology	Fluorescent Immunoassay	Same
Incubation Time	10 minute cycle	Same
Reference range	12.3 ng/mL to 60.0 ng/mL	10.8 to 54.75 ng/mL

Calibrator Set
Similarities and Differences

Parameter	ST AIA-PACK 25-OH Vitamin D Calibrator Set	ST AIA-PACK 25-OH Vitamin D Calibrator Set k123131
Intended use	The ST AIA-PACK 25-OH Vitamin D Calibrator Set is intended for IN VITRO DIAGNOSTIC USE ONLY for the calibration of the ST AIA-PACK 25-OH Vitamin D assay.	Same
Matrix	Human serum	Same
Number of Calibrators	6	Same
Format	Lyophilized	Same
Standardization/Traceability	Traceable to the ID-LC/MS/MS 25 (OH) vitamin D reference measurement procedure (University of Ghent) via patient sample correlation.	Traceable to an Internal reference standard
Concentration 25-OH vit D	Approximately 0-135 ng/mL (0, 8, 17, 33, 66, 135 ng/mL)	Approximately 0-165 ng/mL (0, 10, 20, 40, 80, 165 ng/mL)

PERFORMANCE CHARACTERISTICS

Precision

Precision was assessed by assaying three levels of unaltered serum specimens (Serum-A, Serum-B and Serum-C) and three spiked serum specimens (Serum-D, Serum-E and Serum-F) on two analyzers and two lots of reagents. Estimates of total and within-run precision were obtained from measurements of 2 replicates in a single run, 2 times a day for 20 non-consecutive days. This equaled a total of 40 runs and 80 determinants per lot. In addition, all of the data were combined to assess the within run, between run, between day, between lot and total precision. The following results were obtained when testing for precision:

Within-run precision 1.3 – 3.9%

Between run precision 1.5 – 3,1%

Between day precision 2.2 – 4.1%

Total precision 2.6 – 4.9%

Between lot precision 1.1 – 3.1%

Combined Lot Summary Table

Sample		Serum A	Serum B	Serum C	Serum D	Serum E	Serum F
Mean Conc. ng/mL		16.9	20.9	24.7	55.2	74.6	95.3
Within Run	SD	0.62	0.82	0.77	1.28	1.55	1.24
	%CV	3.7	3.9	3.1	2.3	2.1	1.3

Between Run	SD	0.53	0.65	0.52	1.07	1.26	1.40
	%CV	3.1	3.1	2.1	1.9	1.7	1.5
Between Day	SD	0.64	0.68	1.02	1.48	1.88	2.07
	%CV	3.8	3.3	4.1	2.7	2.5	2.2
Between Lot	SD	0.53	0.36	0.76	1.16	1.57	1.03
	%CV	3.1	1.7	3.1	2.1	2.1	1.1
Total	SD	0.82	0.96	1.19	1.81	2.28	2.43
	%CV	4.9	4.6	4.8	3.3	3.1	2.6

The precision equals or exceeds the precision obtained with the predicate calibrator traceability for (k)123131.

Linearity:

The linearity for ST AIA-PACK 25-OH Vitamin D Calibrator was determined, based on the CLSI protocol entitled: Evaluation of the Linearity of Qualitative Measurement Methods; Approved Guidelines (EP6-A). The linearity was measured on the AIA-2000 instrument and has been demonstrated to be linear from 4.0 ng/mL to 120 ng/mL.

There is no change in linearity from k123131.

Standardization and Traceability

This assay is traceable to the isotope dilution-liquid chromatography/tandem mass spectrometry (ID-LC-/MS/MS) 25-OH Vitamin D Reference Method Procedure (RMP) that is traceable to the National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 2972.

The Tosoh ST-AIA PACK 25 OH Vitamin D assay was originally cleared under 510(k)123131. Tosoh modified the assay by standardizing the cleared Vitamin D assay in accordance with the Vitamin D Standardization and Certification Program (VDSCP).

Please refer to http://ods.od.nih.gov/Research/Vitamin D.aspx for more information on this program.

In accordance with the recommendations of the program, the traceability of the Tosoh ST-AIA PACK 25-OH Vitamin D Calibrator Set was verified by completing a method comparison and bias estimation using the University of Ghent's ID-LC/MS/MS 25-OH vitamin D Reference Measurement Procedure (RMP).

The relationship between the Tosoh ST-AIA PACK 25-OH Vitamin D assay and the ID-LC/MS/MS 25-OH Vitamin D RMP is described below in the method comparison section.

Value Assignment

The values of the primary reference materials were adjusted with correlation study results with the ID-LC-MS/MS method. The values were verified by comparing measured results with those obtained with ID-LC-MS/MS for patient samples at the University of Ghent, in Ghent, Belgium.

The values of the secondary reference material were assigned using the primary reference

materials as calibrators. The values were verified by comparing measured results with those obtained with the previous lot for patient samples.

The commercial calibrator values were assigned with the secondary reference materials as calibrators. The values were verified by comparing measured results with those obtained with the previous lot for control materials.

Correlation

Method Comparison

The methods comparison study was conducted with reference to the CLSI protocol entitled: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP9-A2)

A total of 111 serum specimens in the range of 5.0 -114 ng/mL, as value assigned by the Ghent University ID-LC-MS/MS reference measurement procedure (RMP), were assayed in singleton utilizing the ST AIA-PACK 25-OH Vitamin D assay to assess the ST-AIA-PACK 25-OH Vitamin D Assay traceability to the RMP.
The Weighted Deming regression analysis between the RMP method and the ST AIA-PACK 25-OH Vitamin D Assay is listed below:

	Weighted Deming *
Slope:	0.98 (0.92 – 1.05)
Intercept:	-0.48 (-1.89 – 0.92)
Standard Error Estimate	0.708
Corr Coef (R):	0.965
Bias:	-0.23 (-0.71%)
Points (Plotted/Total):	111/111
Result Ranges:	ST AIA-PACK 25-OH Vitamin D 4.7 to 120 ng/mL ID-LC-MS/MS (Ghent University) 5.0 to 114 ng/mL

*95% Confidence Intervals are shown in parentheses

To demonstrate the bias between the standardized assay (candidate) as compared to the original assay (predicate), one hundred eighty-one (181) unaltered serum specimens were assayed in singleton utilizing the ST AIA-PACK 25-OH Vitamin D assay on the AIA-2000 analyzer using calibrations from ST AIA-PACK 25-OH Vitamin D Calibrator (predicate and candidate) and comparing the results. The results are listed below:

	Deming *	**Regular ***
Slope	0.808 (0.801 to 0.816)	0.807 (0.7999 to 0.815)
Intercept	0.26 (-0.15 to 0.67)	0.33 (-0.08 to 0.73)
Standard Error Estimate	1.17	1.17
Corr Coef ®	0.9979	
Bias	-8.90 (-20.25%)	
Points (Plotted/Total)	181/181	
Result Ranges	Predicate calibrator 11.4 to111.8 ng/mL Candidate calibrator 9.4 to 92.3 ng/mL	

*95% Confidence Intervals are shown in parentheses

Matrix Comparison

See K123131

Cross Reactivity

See k123131

Reference Ranges

A reference range study was conducted based on guidance from Clinical and Laboratory Standards Institute (CLSI) Protocol C28-A3.

To determine the reference range for the ST-AIA-PACK 25-OH Vitamin D Assay, a total of 252 serum samples, from 111 females and 141 males, ages 21 to 86 years, were assayed in singleton utilizing the ST AIA-PACK 25-OH Vitamin D assay on the AIA-2000 analyzer. The specimens were obtained from apparently healthy individuals with normal PTH, TSH, calcium, magnesium and phosphorus levels. The samples were collected in Maryland, Pennsylvania, Wisconsin and Southern California in March, May, June, and July respectively.

The reference range specimens had a normal distribution and the 95% confidence interval was defined as the ref. range interval.

Demographics

Caucasian	48%	non-Caucasian	52%
Female	44%	Male	56%

Supplements	26%	No Supplements	56%	Not specified	18%

There was no significant difference between values obtained for male and females. The following reference range was obtained for the adult population:

Number of Samples (n)	252
Reference Interval	12.3 – 60.0 ng/mL

Interference

See k123131

Limit of Detection and Limit of Quantification

The LoB and LoD of the ST AIA-PACK 25-OH Vitamin D was determined based on the CLSI guideline entitled: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline EP17-A.

The LoB was determined by 60 measurements of 3 different blank specimens. The LoB was the value at the 95th percentile. In this case the LoB was determined to be 1.6 ng/mL.

The LoD was determined by 12 measurements of 5 low level samples. The sample range was chosen to be between LoB and 4xLoB and 3 lots of reagents were utilized. The LoD was determined to be 3.2 ng/mL.

The LoQ was determined by measuring a series of low Vitamin D samples that were prepared by diluting a specimen with known Vitamin C concentration at different dilution ratios. The prepared samples were assayed in replicates of eight 98) every day for five (5) days on one instrument for a total of 40 replicates per sample.

The mean, SD and %CV were established and plotted to calculate the functional sensitivity. The functional sensitivity is 3.3 ng/mL at 20% CV.

Standards:

Number	FDA Recognition Number	Revision Date	Title
EP5-A2	7-110	10/31/2005	Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition
EP6-A	7-193	03/18/2009	Evaluation of the Linearity of Quantitative Measurement Procedures: a Statistical Approach: Approved Guideline
EP28-A3	7-224	09/08/2009	Defining, Establishing, and verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition
EP17-A	7-194	03/18/2009	Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline
EP9-A3	7-92	03/08/2004	Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Second Edition

Conclusion:

The Tosoh Bioscience, Inc. ST AIA-PACK 25-OH Vitamin D Assay and Calibrator Set is substantially equivalent to the Tosoh k123131- ST AIA-PACK 25-OH Vitamin D Assay and Calibrator Set for in vitro diagnostic use only for the quantitative measurement of total 25-hydroxyvitamin D (25-OH Vitamin D) in human serum, Na heparinized or EDTA plasma on Tosoh AIA System Analyzers.